REMARKS

The Office Action dated April 27, 2007 has been reviewed and the comments of the U.S. Patent and Trademark Office have been considered. The following remarks are respectfully submitted to place the application in condition for allowance.

1 Summary of Claims

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim remain under examination in the application, is presented, with an appropriate defined status identifier. Claims 48 and 107-145 are pending. Claims 139-145 are withdrawn. Claims 1-47 and 49-106 were canceled previously.

By this amendment, Applicants have amended claims 48, 107, 110, 111, 120, 121, 124-131, 133-140 and 145. Applicants have cancelled claims 108, 109, 112, 113, 137 and 141-144. Also, Applicants have added claims 146-152.

The subject application is a continuation of U.S. Serial No. 09/646,807, filed December 5, 2000 (the "'807 Application"), which is the U.S. National Phase under 35 U.S.C. § 371 of International Application PCT/AU99/00195, filed March 19, 1999, which is a continuation-in-part of U.S. Serial No. 09/100,812, filed June 19, 1998 (the "'812 Application"), now U.S. Patent No. 6,573,099 B2, issued June 3, 2003, and claims priority of Australian Provisional Patent Application No. PP2499 (the "Priority Application") and PP2492, filed March 20, 1998.

Support for the amendments to claims 48, 110 and 133 can be found, *inter alia*, at page 29, lines 23 to 29, page 27, lines 23 to 29, page 8, line 21 to page 9, line 3, page 21, lines 23 to 28, page 7, line 17, page 33, lines 12 to 17, and page 33, lines 19 to 29 of the subject application.

Support for the amendment to each of claims 107 and 111 can be found, *inter alia*, at page 15, lines 12 to 29 of the subject application.

Support for the amendment to each of claims 120, 121, 128, 129, 130, 131, 134, 135, 139, 140, and 145 can be found, *inter alia*, at page 7, line 17 and page 17, line 1 of the subject application.

Support for the amendment to each of claims 124 to 127 can be found, *inter alia*, at page 8, line 24 to page 9, line 3, page 20 lines 3 to 7 of the subject application.

Support for the amendment to each of claims 136 and 138 can be found, *inter alia*, at page 7, line 17, page 17, line 1 and page 33, lines 12 to 29 of the subject application.

Support for new claims 146 to 148 may be found, *inter alia*, in the subject application and '807 application on page 7 lines 15 to 16 and in the Priority Application on page 7 lines 11 to 17.

Support for new claim 149 may be found, *inter alia*, in the subject application and '807 application on page 19 lines 22 to 25 and in the Priority Application on page 9 lines 24 to 25.

Support for new claims 150 to 152 may be found, *inter alia*, in the subject application and '807 application on page 24 lines 5 to 21 and in the Priority Application on page 14 line 17 to page 15 line 2.

For completeness of the record, in regard to amended claims 48, 110 and 133:

the element "synthetic gene" is disclosed, *inter alia*, in the '807 application on page 27 lines 7 to 9 and in the Priority Application on page 16 lines 5 to 9;

the element "multiple structural gene regions" is disclosed, *inter alia*, in the '807 application on page 29 lines 23 to 29 and in the Priority Application on page 17 lines 15 to 20;

the element "structural gene region" is disclosed, *inter alia*, in the '807 application on page 27 lines 23 to 26 and in the Priority Application on page 16 line 29 to page 17 line 13;

the element "comprises a nucleotide sequence" is disclosed, *inter alia*, in the '807 application on page 6 lines 12 to 18 and in the Priority Application on page 16 lines 5 to 9;

the element "consists of greater than 20 consecutive nucleotides" is disclosed, *inter alia*, in the '807 application on page 8 lines 21 to 24 and in the Priority Application on page 25 lines 20 to 23;

the element "which is identical to a particular nucleotide sequence of a target gene" is disclosed, *inter alia*, in the '807 application on page 6 lines 12 to 18 and page 21 lines 23 to 28 and in the Priority Application on page 11 lines 14 to 18, and page 17, line 19;

the element "a vertebrate animal cell" is disclosed, *inter alia*, in the '807 application on page 7 line 17 and in the Priority Application on page 7 line 15;

the element "in the sense orientation" is disclosed, *inter alia*, in the '807 application on page 33 lines 12 to 17 and in the Priority Application on page 21 lines 10 to 13;

the element "in the antisense orientation" is disclosed, *inter alia*, in the '807 application on page 33 lines 19 to 29 and in the Priority Application on page 21 lines 15 to 20;

the element "operably under the control of a single promoter sequence" is disclosed, *inter alia*, in the '807 application on page 27 lines 24 to 29 and in the Priority Application on page 17 lines 2 to 4;

the element "which is operable in the cell" is disclosed, *inter alia*, in the '807 application on page 33 lines 7 to 10 and in the Priority Application on page 16 lines 5 to 11;

the element "arranged as an interrupted palindrome sequence" is disclosed, *inter alia*, in the '807 application on page 29 lines 25 to 29 and in the Priority Application on page 17 lines 17 to 20;

In addition to the support mentioned above for claim 48, claim 110 is supported:

the element "synthetic genetic construct" is disclosed, *inter alia*, in the '807 application on page 36 line 30 to page 37 line 3 and in the Priority Application on page 16 lines 5 to 11;

the element "a genetic sequence which provides for the maintenance and/or replication of the genetic construct in prokaryotes or eukaryotes and/or the integration of the genetic construct or a part thereof into the genome of a eukaryotic cell or organism" is disclosed, *inter alia*, in the '807 application on page 38 lines 16 to 20 and in the Priority Application on page 23 lines 17 to 20.

2. Election/Restrictions

The Examiner withdrew claims 139-145 from further consideration pursuant to 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention. Applicants added the claims by amendment filed on February 28, 2007. The Examiner noted that Applicants timely traversed the restriction requirement in the reply filed on December 15, 2004.

3. Priority Under 35 U.S.C. § 120

The Examiner acknowledged Applicants' claim for the benefit of a prior-filed application under 35 U.S.C. § 119(e) or under 35 U.S.C. §§ 120, 121, or 365(c). The Examiner asserted, however, that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120. Specifically, the Examiner stated that the

disclosure of the invention in the parent application and in the later- filed application do not comply with the requirements of the first paragraph of 35 U.S.C. § 112, citing *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). The Examiner alleged that the disclosure of the prior-filed applications, Application No. 09/100,812 (Patent No. 6,573,099) and 09/646,807, fail to provide adequate support or enablement for instant claims 48 and 107-138 "under 112 first paragraph for 'structural gene sequence having greater than 20 consecutive nucleotides which is identical in sequence to greater than 20 consecutive nucleotides of a genus of target gene or region thereof and wherein multiple copies of the nucleotide sequence are arranged in the structural gene region in an interrupted palindrome sequence.[sic]"

The Examiner continued by stating "[t]he specification of '812 contemplates: 'at least about 20-30 nucleotides in length derived from a viral DNA polymerase, viral RNA polymerase…' and 'the structural gene component of the synthetic gene comprises at least about 20-30 nucleotides in length….'"

In addition, the Examiner stated "the specification of '812 only discloses: 'In a more particularly preferred embodiment of the invention, the multiple structural gene comprises an interrupted direct repeat or interrupted palindrome comprising two identical or substantially-identical BEV polymerase structural gene sequences or alternatively, two identical or substantially-identical tyrosinase structural gene sequences or a homologue, analogue or derivative thereof separated by a stuffer fragment comprising a nucleotide sequence which encodes green-fluorescent protein or a biologically-active analogue or derivative thereof.'"

The Examiner further alleged that the claims do not have written support in application '807 for a "genus of nucleotide sequences of greater than 20 nucleotides which is identical to the sequence of the target gene or region thereof." Finally, the Examiner alleged that claim 48 and

claims dependent therefrom do not have written support in the Australian Provisional Applications PP2492 and PP2499 "for the limitation 'a structural gene region which comprises multiple copies of a nucleotide sequence of greater than 20 consecutive nucleotides which is identical to the sequence of the target gene or region thereof' and 'wherein the multiple copies of the nucleotide sequence are arranged in the structural gene region in an interrupted palindrome sequence.'"

Applicants' Response

Applicants respectfully traverse the alleged suggestion that the '807,'812 and Priority Applications fail to support the currently amended claimed invention under 35 U.S.C. § 120. M.P.E.P. § 2163 indicates that "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." (emphasis added; citations omitted). Applicants maintain that each of the priority applications satisfies this requirement.

Applicants point to the disclosure in each of the present application and the '807 Application at page 6, lines 12-18, page 7, line 17, page 8, lines 21-24, page 21, lines 23-28, and Priority Application PP2499 at page 7, line 15, page 16, lines 5-9, page 17, line 19, page 25, lines 20-23, page 11, lines 14-18, for the teaching of the feature "nucleotide sequence which consists of greater than 20 consecutive nucleotides which is identical to a particular nucleotide sequence of a target gene in a vertebrate animal cell." It is clear from these passages that the disclosure of the "nucleotide sequence of a target gene" is in the context of any target gene in the

vertebrate animal cell, *i.e.,* it is not limited to the species of target gene "viral DNA polymerase, viral RNA polymerase..." as referred to by the Examiner (Office Action, page 3).

For completeness of the record, in regard to amended claims 48, 110 and 133:

the element "synthetic gene" is disclosed, *inter alia*, in the '807 application on page 27 lines 7 to 9 and in the Priority Application on page 16 lines 5 to 9;

the element "multiple structural gene regions" is disclosed, *inter alia*, in the subject application and the '807 application on page 29 lines 23 to 29 and in the Priority Application on page 17 lines 15 to 20;

the element "structural gene region" is disclosed, *inter alia*, in the subject application and the '807 application on page 27 lines 23 to 26 and in the Priority Application on page 16 line 29 to page 17 line 13;

the element "comprises a nucleotide sequence" is disclosed, *inter alia*, in the subject application and the '807 application on page 6 lines 12 to 18 and in the Priority Application on page 16 lines 5 to 9;

the element "consists of greater than 20 consecutive nucleotides" is disclosed, *inter alia*, in the subject application and the '807 application on page 8 lines 21 to 24 and in the Priority Application on page 25 lines 20 to 23;

the element "which is identical to a particular nucleotide sequence of a target gene" is disclosed, *inter alia*, in the subject application and the '807 application on page 6 lines 12 to 18 and page 21 lines 23 to 28 and in the Priority Application on page 11 lines 14 to 18, and page 17, line 19;

the element "a vertebrate animal cell" is disclosed, *inter alia*, in the subject application and the '807 application on page 7 line 17 and in the Priority Application on page 7 line 15;

the element "in the sense orientation" is disclosed, *inter alia*, in the subject application and the '807 application on page 33 lines 12 to 17 and in the Priority Application on page 21 lines 10 to 13;

the element "in the antisense orientation" is disclosed, *inter alia*, in the subject application and the '807 application on page 33 lines 19 to 29 and in the Priority Application on page 21 lines 15 to 20;

the element "operably under the control of a single promoter sequence" is disclosed, *inter alia*, in the subject application and the '807 application on page 27 lines 24 to 29 and in the Priority Application on page 17 lines 2 to 4;

the element "which is operable in the cell" is disclosed, *inter alia*, in the subject application and the '807 application on page 33 lines 7 to 10 and in the Priority Application on page 16 lines 5 to 11;

the element "arranged as an interrupted palindrome sequence" is disclosed, *inter alia*, in the subject application and the '807 application on page 29 lines 25 to 29 and in the Priority Application on page 17 lines 17 to 20;

In addition to the support mentioned above, claim 110 is supported:

the element "synthetic genetic construct" is disclosed, *inter alia*, in the subject application and the '807 application on page 36 line 30 to page 37 line 3 and in the Priority Application on page 16 lines 5 to 11; and

the element "a genetic sequence which provides for the maintenance and/or replication of the genetic construct in prokaryotes or eukaryotes and/or the integration of the genetic construct or a part thereof into the genome of a eukaryotic cell or organism" is disclosed, *inter alia*, in the

subject application and the '807 application on page 38 lines 16 to 20 and in the Priority Application on page 23 lines 17 to 20.

In summary, each of the elements of the pending claims is described and/or defined. Applicants therefore maintain that each of the subject specification, the '807 Application and the Priority Application fully describe the claimed invention, as required by M.P.E.P. § 2163. Currently amended claims 48, 107, 111, 114-136 and 138 have priority to the '807 and Australian Provisional PP2499 applications.

4. Information Disclosure Statement

Applicants thank the Examiner for acknowledgement and consideration of the two exhibits from civil litigation related to the priority document U.S. 6.573,099 that Applicants submitted in the Information Disclosure Statement on March 5, 2007. The Examiner did not consider the documents cited in the Exhibits, which list over 4500 references submitted by adverse parties during the litigation. Applicants submitted the lists in the present application to comply with the ethical duty to disclose all information to the US Patent and Trademark Office. Applicants have examined only the lists of titles for references known to Applicants and provided to the Examiner. Other than those that have been submitted in Information Disclosure Statements in the present application, Applicants have no reason to believe that the references in the list are material to the claimed invention and have no reason to believe that, even if material, any of the references would not be cumulative in light of the references already submitted during the prosecution of the present application.

5. Claim Rejections Under 35 USC § 112

Rejections of Claims 110-119, 121, 123, 125, 127, 129, 131 and 132 under 35 USC § 112, first paragraph

The Examiner rejected claims 110-119, 121, 123, 125, 127, 129, 131 and 132 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserted that the claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner alleged that there does not seem to be support for the limitation 'a synthetic genetic construct comprising a synthetic gene and a genetic sequence which provides for the maintenance and/or replication of the genetic construct in prokaryotes or eukaryotes and/or the integration of the genetic construct or a part thereof into the genome of a eukaryotic cell or organism' in claim 110 and claims dependent therefrom. The Examiner alleged this was new matter.

Applicants' Response

Applicants respectfully traverse the rejection. The M.P.E.P. § 2163 indicates that "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in *sufficient detail* that one skilled in the art can *reasonably conclude* that the inventor had possession of the claimed invention." (emphasis added; citations omitted).

Applicants submit that the element "synthetic genetic construct" is disclosed, *inter alia*, in the subject application and the '807 application on page 36 line 30 to page 37 line 3 and in the Priority Application on page 16 lines 5 to 11. The element "a genetic sequence which provides for the maintenance and/or replication of the genetic construct in prokaryotes or eukaryotes and/or the integration of the genetic construct or a part thereof into the genome of a eukaryotic

cell or organism" is disclosed, *inter alia*, in the subject application and the '807 application on page 38 lines 16 to 20 and in the Priority Application on page 23 lines 17 to 20. Clearly, the claimed invention is described in sufficient detail that one skilled in the relevant art can reasonably conclude that the inventors had possession of the claimed invention at the time the application was filed.

Applicants respectfully request withdrawal of the rejection of the rejected claims for lack of written description under 35 U.S.C. § 112, first paragraph.

Rejections of Claims 48 and 107-138 under 35 USC § 112, first paragraph

The Examiner rejected claims 48 and 107-138 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleged that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner alleged that claims 48 and 107-138, as best understood, are readable on a genus of structural gene region which comprises multiple copies of a nucleotide sequence of greater than 20 consecutive nucleotides which is identical to the sequence of the target gene or region thereof, wherein the genus of structural gene sequences is not claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made.

The Examiner alleged that the specification contemplates a target gene which is endogenous to an animal cell or a foreign gene such as a viral or foreign genetic sequence (page 7). The Examiner alleged that the disclosure provides sufficient description for the target gene is

α-1,3-galactosyltransferase. The Examiner alleged that the specification further provides support for a structural gene component of the synthetic gene comprises derived from the BEV RNA-dependent RNA polymerase gene or the murine tyrosinase gene or the *Escherichia coli* lac repressor gene lacI.

The Examiner alleged that the specification does not provide sufficient description of a genus of a structural gene sequence comprises a nucleotide sequence that is identical to the sequence of the target gene or region thereof and is capable of post-transcriptionally delaying, repressing or otherwise reducing the expression of a target gene in a human cell. The Examiner alleged that there is a variation between the species embraced by the claimed genus and function.

Applicants' Response

In response, Applicants respectfully traverse the rejection. To advance prosecution, however, Applicants have amended the pending claims to no longer recite the functional language to which the April 27, 2007 Office Action objected. The rejection is therefore believed to be moot.

As discussed above, "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in *sufficient detail* that one skilled in the art can *reasonably conclude* that the inventor had possession of the claimed invention." (emphasis added; citations omitted). M.P.E.P. § 2163. There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims"). M.P.E.P. §

2163. The specification of the subject application describes in sufficient detail the characteristics of the structural gene regions comprising nucleotide sequences recited in the claims. Upon selecting a target gene, one of ordinary skill in the art using no more than general knowledge in the art would readily contemplate the identical nucleotide sequences within the metes and bounds of the now pending claims.

The invention claimed in amended claim 48 is a synthetic gene, comprising multiple structural gene regions, wherein each structural gene region comprises a nucleotide sequence which consists of greater than 20 consecutive nucleotides and which is identical to a particular nucleotide sequence of a target gene in a vertebrate animal cell. One of the structural gene regions is placed in the sense orientation and another of the structural gene regions is placed in the antisense orientation operably under the control of a single promoter sequence which is operable in the cell. The structural gene region placed in the sense orientation and the structural gene region placed in the antisense orientation are arranged as an interrupted palindrome sequence which is operably under the control of the single promoter sequence. The invention claimed in amended claim 110 is a synthetic genetic construct comprising the synthetic gene described in claim 48. The claimed invention is supported in the specification for making the synthetic gene and synthetic genetic construct using a nucleic acid sequence that is highly specific to a target gene in a vertebrate animal cell.

The genus of nucleotide sequences in the claimed synthetic genes is defined by the metes and bounds of the claim, based on the description in the specification. Applicants respectfully submit that the person of ordinary skill in the art would readily conclude that the genus claimed was contemplated by Applicants in the application. M.P.E.P. § 2164.01 provides that "[a] patent need not teach, and preferably omits, what is well known in the art" (citations omitted). Viral

genes and other target genes of vertebrate animal cells are well known in the art, as are methods of obtaining nucleotide sequences of such genes. It is unreasonable for Applicants to list every known gene that could be a target by the claimed method. Such is unnecessary because one of skill in the art would readily envision each and every nucleotide sequence of Applicants' claimed invention upon selecting a desired gene to target based on the description in the specification. The application, when combined with no more than general knowledge in the art, describe the claimed invention in such a manner that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention, as required by M.P.E.P. § 2163.

The Examiner stated "[t]he skilled artisan cannot envision the detailed structure of a genus of structural genes that must exhibit the contemplated biological functions." (page 8). In response, without conceding the correctness of the Examiner's position and to expedite prosecution, Applicants have amended the pending claims to no longer recite the functional language to which the April 27, 2007 Office Action rejected.

One of skill in the art at the time the invention was made would therefore recognize that Applicants were in possession of the claimed invention as presently claimed. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Rejections of Claims 108, 109, 112, and 137under 35 USC § 112, second paragraph

The Examiner rejected claims 108, 109, 112, and 137 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserted that the term "from greater than" in claims 108, 109, 112, and 137 is a relative term which renders the claim

indefinite.

Applicants' Response

Without agreeing with the Examiner's assertion and merely to further prosecution of the application, Applicants have cancelled claims 108, 109, 112, and 137. Thus, the rejection of those claims is moot. Applicants request that the Examiner withdraw the rejection under 35 U.S.C. § 112, second paragraph.

6. Claim Rejections under 35 USC § 102 (e)

Anticipation of claims 48, 107, 108, 110, 111, 112, 114, 115, 116, 117, 118, 120, 121, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, and 137

The Examiner rejected Claims 48, 107, 108, 110, 111, 112, 114, 115, 116, 117, 118, 120, 121, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, and 137 under 35 U.S.C. § 102(e) as being anticipated by Fire *et al.,* (U.S. 6,506,559) ("Fire"). The Examiner asserted that Fire teaches a vector comprising a construct comprising a promoter operably linked to a nucleotide sequence comprising dsRNA comprising a sense strand and an antisense strand of the target gene (columns 4 and 9), the dsRNA may be formed by a single self-complementary RNA strand or two complementary RNA strands (column 7), the construct. comprises a regulatory region including polyadenylation (columns 8-9), the nucleotide sequence may be at least 25 or 50 bases (column 8), the vector can be introduced into a cancerous cell, including cancer cells find in humans (columns 9-10), a viral vector or lipid mediated carrier transport can be used as the vector (column 9), the cell can comprise a target gene at risk from a pathogen including HIV or can be from several different types of animals (columns 4, 8, and 10), and the construct can

comprise a structural gene with an intron. The Examiner further asserted that the structural gene can comprise a 5' or 3' untranslated region (column 20), and the structural gene can comprise one or more strands of the nucleotide sequence (column 4).

Applicants' Response

Applicants respectfully traverse the rejection and request reconsideration based on the following comments.

To find anticipation under 35 U.S.C. § 102, every element of the claims must be taught in a single reference. M.P.E.P. § 2131; *See, e.g., Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 138 (Fed. Cir. 1986). Applicants submit that Fire does not teach all of the elements of amended claims 48, 110 and 133 and the claims that depend from them, specifically at least the elements of 1) "a synthetic gene comprising multiple structural gene regions, wherein each structural gene region comprises a nucleotide sequence which consists of greater than 20 consecutive nucleotides identical to a particular nucleotide sequence of a target gene" and 2) "the structural gene region placed in the sense orientation and the structural gene region placed in the antisense orientation are arranged as an interrupted palindrome sequence". Furthermore, Fire does not teach a vertebrate animal cell in cell or tissue culture comprising a synthetic gene with the elements as claimed.

Merely to further prosecution of this application, and without prejudice, Applicants have cancelled claims 108, 109, 112, 113, 137, 141-144. Thus, Applicants submit that the rejection related to those claims is moot.

The Examiner stated that Fire teaches that the structural gene comprising nucleotide sequence can comprise one or more strands, which would read on multiple copies of the

nucleotide sequences. Applicants disagree. Fire teaches the double-stranded structure may be formed by a single self-complementary RNA strand or two complementary RNA strands. (Column 7, lines 42-44). The sequences within the "single self-complementary RNA strand" that are self complementary and the "two complementary RNA strands" that Fire discloses are by definition a sequence and its complement and are not the same as multiple copies of an identical nucleotide sequence.

The Examiner stated Fire teaches an interrupted palindrome sequence because the arrangement reads on placing the nucleotide sequences in antisense and sense orientation. (Office Action at page 12). Again, Applicants respectfully disagree. A synthetic gene comprising a structural gene region placed in the sense orientation and another structural gene region placed in the antisense orientation arranged as an interrupted palindrome sequence, as presently claimed, is not a "single self-complementary RNA strand" or "two self-complementary strands." The Examiner states that the skilled artisan understands the term "interrupted palindrome sequence" as an arrangement of the sequences with a "stuffer" between them. (Office Action at page 10). In the Office Action, the Examiner has not pointed to any disclosure of a stuffer fragment in Fire. Indeed, the Examiner has explicitly stated in the same Office Action (page 15) that "Fire does not specifically teach separating a construct comprising the structural gene sequences with a stuffer sequence." Essentially similar statements have been made by the Examiner in examination of related patent application 10/346,853 and in the re-examination of US Patent No. 6,573,099. Therefore, Fire does not teach multiple genetic regions arranged as an interrupted palindrome sequence. Moreover, the use of stuffer fragments has led to unexpectedly beneficial effects in production and use of the claimed invention.

In addition to the elements listed above, Fire does not disclose another element in claim 110, namely "a genetic sequence which provides for the maintenance and/or replication of the genetic construct in prokaryotes or eukaryotes and/or the integration of the genetic construct or a part thereof into the genome of a eukaryotic cell or organism". Fire does not teach a structural gene region in sense orientation and a structural gene region in antisense orientation separated by a sequence of nucleotides, in particular a sequence of a given length such as 10-50 nucleotides, 50-100 nucleotides or 100-500 nucleotides. Fire does not disclose a retroviral vector.

Clearly, Fire does not teach each and every element of instant claims 48, 110 and 133 or the arrangement of those elements as recited in the claims. Applicants have added new claims 146-152, which incorporate all of the limitations of amended claim 48, 110 and 133. Therefore, Fire does not anticipate the newly presented claims.

Further, Applicants maintain that Fire is not a valid prior art reference under 35 U.S.C. § 102 in regard to the subject application. Applicants note that the effective filing date of the subject application for the material claimed is March 20, 1998. Fire issued from an application filed December 18, 1998, *i.e.,* long after the first effective filing date of the subject application.

Fire claims the benefit of U.S. Provisional Application No. 60/068,562, filed December 23, 1997 (the "Fire Provisional"). The Fire Provisional, however, discloses less than the Fire patent. Any rejection under 35 U.S.C. § 102(e) can only be based on the disclosure of the Fire Provisional, not on the disclosure of the Fire patent. Applicants point out that the Fire Provisional discloses less than Fire, and therefore cannot disclose at least each of the elements 1) "a synthetic gene comprising multiple structural gene regions", 2) "a synthetic genetic construct comprising a synthetic gene comprising multiple structural gene regions", 3) "structural gene region comprises a nucleotide sequence which consists of greater than 20 consecutive

nucleotides" and 4) "the structural gene region placed in the sense orientation and the structural gene region placed in the antisense orientation are arranged as an interrupted palindrome sequence".

While this itself should remove Fire as a reference, there are further reasons that Fire is an inappropriate reference. Applicants respectfully point out that the claimed invention was invented before the filing date of Fire, and before the filing date of the Fire Provisional. Applicants attach hereto as **Exhibit B and Exhibit C** copies of Declarations under 37 C.F.R. § 1.131 submitted in connection with U.S. Reexamination No. 90/007,247, the re-examination of the patent that issued from the '812 Application. As indicated in the declarations and accompanying exhibits, Applicants' invention was prior to the filing of the Fire Provisional. Fire is thereby removed as an effective prior art reference.

Applicants submit that Fire does not anticipate the claimed invention and respectfully request withdrawal of the rejection of under 35 U.S.C. § 102 (e).

7. Claim Rejections under 35 USC 103

The Examiner rejected claims 48, 107-111, 113, 117, 119 and 122-123 under 35 U.S.C. 103(a) as being unpatentable over Fire et al (U.S. 6,506,559) ("Fire") taken with other references, specifically:

> claims 110, 107, 109, 110, 111, 113, were rejected as being unpatentable over Fire taken with Dietz (U.S. 5,814,500) ("Dietz"); and
>
> claims 48, 107, 138, and 151 were rejected as being unpatentable over Fire taken with Ladner *et al.* (U.S. 5,198,346) ("Ladner").

The Examiner asserted that Fire teaches a vector comprising a construct comprising a promoter operably linked to a nucleotide sequence comprising dsRNA comprising a sense strand and an antisense strand of the target gene (columns 4 and 9), the dsRNA may be formed by a single self-complementary RNA strand or two complementary RNA strands (column 7), the construct comprises a regulatory region including polyadenylation (columns 8-9), the nucleotide sequence may be at least 25 or 50 bases (column 8), the vector can be introduced into a cancerous cell, including cancer cells found in humans (columns 9-10), a viral vector or lipid mediated carrier transport can be used as the vector (column 9), the cell can comprise a target gene at risk from a pathogen including HIV or can be from several different types of animals (columns 4, 8, and 10), the target gene can be an endogenous in a human cell (columns 4 and 10-11), the construct can comprise a structural gene with an intron. The Examiner further asserted that the structural gene can comprise a 5' or 3' untranslated region (column 20), and the structural gene can comprise one or more strands of the nucleotide sequence (column 4).

In levying an obviousness rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing that the prior art references, when combined, teach or suggest all the claim limitations. M.P.E.P. §2143; *see also, In re Royka*, 490 F.2d 981 (C.C.P.A. 1974). To determine obviousness, Examiners must consider (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the pertinent art, and (4) objective evidence relevant to the issue of obviousness." *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). In addition, the Supreme Court has noted that there must be a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the new invention does. *KSR International Co. v. Teleflex*

Inc., 550 U.S. __, 82 USPQ2d 1385 (2007). Here, the Examiner has not met the burden of showing obviousness.

Rejections of Claims 110, 117, 119 and 122-123 as Obvious over Fire with Dietz (US 5,814,500)

The Examiner rejected claims 110, 117, 119 and 122-123 under 35 U.S.C. 103(a) as being unpatentable over Fire taken with Dietz (US 5,814,500). The Examiner acknowledged that Fire does not specifically teach a retroviral vector comprising the dsRNA construct. The Examiner asserted, however, that Dietz teaches making a retroviral vector for expressing inhibiting RNA (column 8). The Examiner asserted that Dietz further teaches using a SV40 early, RSV or CMV promoter to express the RNA (column 6).

The Examiner asserted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Dietz to produce a retroviral vector comprising the dsRNA construct. and produce a dsRNA construct comprising a CMV, SV40 early, or RSV promoter.

Applicants' Response

Applicants respectfully traverse the rejection.

As noted above, Applicants point out that Fire is not prior art against the subject application and this rejection is defective based on this threshold issue.

Further, Fire does not teach all the elements of the present invention in claims 48 and 110, let alone dependent claims 117, 119 and 122-123. Specifically, Applicants maintain that at least 1) "a synthetic gene comprising multiple structural gene regions, wherein each structural

gene region comprises a nucleotide sequence which consists of greater than 20 consecutive nucleotides which is identical to a particular nucleotide sequence of a target gene" and 2) "the structural gene region placed in the sense orientation and the structural gene region placed in the antisense orientation are arranged as an interrupted palindrome sequence" are not taught by the references.

Moreover, the deficiencies of Fire are not cured by Dietz related to the limitation of a retroviral vector or SV40 early, RSV or CMV promoter. Applicants note that claims 48 and 110 do not recite a retroviral vector or SV40 early, RSV or CMV promoter. Dietz teaches a nucleic acid construct for delivery of antisense targeting sequences. Dietz does not teach a structural gene region placed in the sense orientation and another of the structural gene regions placed in the antisense orientation operably under the control of a single promoter sequence, and wherein the structural gene region placed in the sense orientation and the structural gene region placed in the antisense orientation are arranged as an interrupted palindrome sequence which is operably under the control of the single promoter sequence. One of skill in the art would not be motivated to combine Fire, which also does not teach these elements, with the promoters or the retroviral vectors taught by Dietz in antisense constructs to produce the dsRNA constructs of the present invention.

Dietz is non-analogous art to interfering RNA. There are fundamental differences in antisense and interfering RNA technologies. Antisense is directed to binding RNA and creating a molecule that is not transcribed. Interfering RNA induces a system to cut RNA into smaller pieces for use in affecting gene expression. There is no indication in the art that modification of antisense technology that binds RNA would work for interfering RNA. This is recognized in the field of molecular biology in the interfering RNA technology was such a revolutionary change in

the way those of skill in the art were thinking of affecting gene expression. Moreover, Fire itself claims its dsRNA is different and distinct to antisense sequences, and improvement over antisense in both its fundamental approach and its mode of action: "The present invention differs from antisense-mediated interference in both approach and effectiveness." Fire, column 3, lines 19-20. One of skill in the art would not be motivated to combine the teachings of antisense nucleic acid constructs of Dietz with the dsRNA of Fire to produce a synthetic gene or synthetic genetic construct according to claims 48 and 110 and the depending claims. Applicants respectfully submit that the combination of these two references is inappropriate and suspect.

Most importantly, there is no technical basis from which one of skill in the art could have expected that modifying either reference to include a synthetic gene or synthetic genetic construct comprising multiple genetic regions arranged in an interrupted palindrome orientation under the control of a SV40 early, RSV or CMV promoter. Certainly the teachings of Dietz relating to antisense nucleic acid construct using retroviral vectors and specific promoters do not offer the technical basis; Fire do not suggest that their technology could include multiple structural gene regions placed in the sense orientation and antisense orientation arranged as an interrupted palindrome sequence, let alone any advantage in doing so; and the April 27, 2007 Office Action offers no technical basis for concluding that one of skill would expect success in an interrupted palindrome sequence orientation. Absent such a technical basis, an obviousness rejection cannot be proper. *KSR Int'l v. Teleflex, Inc.*, 550 U.S. ___ (2007).

Accordingly, Applicants maintain that each of claims 110, 117, 119 and 122-123 is patentable over Fire taken with Dietz and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Finally, as detailed above, Applicants respectfully point out that the claimed invention was invented before the filing date of Fire, and before the filing date of the Fire Provisional. As indicated in the Declarations, Applicants invented their invention prior to the filing of the Fire Provisional. This reference is therefore removed as prior art.

Rejections of Claims 48, 107, 109, 110, 111 and 113 as Obvious over Fire with Ladner *et al.* (US 5,198,346)

The Examiner rejected claims 48, 107, 109, 110, 111 and 113 under 35 U.S.C. § 103(a) as being unpatentable over Fire taken with Ladner. The Examiner acknowledged that Fire does not specifically teach separating a construct comprising the structural gene sequences with a stuffer sequence. The Examiner asserted, however, that Ladner teaches using a stuffer fragment having above about 10 nucleotides to introduce a stop codon or a unique restriction site (column and Table 704).

Applicants' Response

Applicants respectfully traverse the rejection.

As noted above, Applicants point out that Fire is not prior art against the subject application and this rejection is defective based on this threshold issue.

Further, Fire does not teach all the elements of the present invention in claims 48 and 110 or dependent claims. Specifically, Applicants maintain that at least 1) "a synthetic gene comprising multiple structural gene regions, wherein each structural gene region comprises a nucleotide sequence which consists of greater than 20 consecutive nucleotides which is identical to a particular nucleotide sequence of a target gene" and 2) "the structural gene region placed in

the sense orientation and the structural gene region placed in the antisense orientation are arranged as an interrupted palindrome sequence" are not taught by the references.

Additional art to incorporate the dependent limitations would not render obvious dependent claims.

Furthermore, the deficiencies of Fire are not cured by Ladner for the elements listed above or a sequence of nucleotides separating the structural gene regions in the sense and antisense orientation arranged as an interrupted palindrome as in claims 107 and 111. Merely to advance prosecution of the application and without prejudice, Applicants have cancelled claims 109 and 113. Therefore, the rejection of claims 109 and 113 is rendered moot. Ladner teaches using a transcription termination sequence and a promoter to regulate transcription of the gene (column 136). In response, Applicants submit that Ladner does not disclose a synthetic gene or synthetic genetic construct comprising multiple structural gene regions where a structural gene region placed in the sense orientation and a structural gene region placed in the antisense orientation are arranged as an interrupted palindrome sequence and separated by a stuffer fragment.

Ladner describes the generation of DNA-binding proteins obtained by variation of genes producing known binding proteins, and production and selection of these proteins in prokaryotic cells. Ladner does not contemplate use of dsRNA genetic constructs in animal cells, as taught by Applicants' presently claimed invention. Indeed, Ladner is about production (overexpression) of DNA-binding proteins, not down-regulation of gene expression. Ladner also is about production of proteins in prokaryotic cells, not eukaryotic animal cells. The Examiner's assertions that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Ladner to produce a construct

comprising a structural gene with a stuffer sequence or an isolated animal cell comprising the construct are incorrect. One of ordinary skill in the art would not be motivated to combine the teachings of production of DNA binding proteins in prokaryotic cells to the use of dsRNA inhibition of gene expression in eukaryotic cells and certainly not in animal cells. Applicants respectfully submit that the combination of these two references is therefore inappropriate. Indeed, the references actually teach away from each other.

One of ordinary skill in the art would not have been motivated to combine the teaching to produce a synthetic gene, as well as a construct comprising a synthetic gene, comprising multiple gene regions with a stuffer sequence.

Most importantly, there is no technical basis from which one of skill in the art could have expected that modifying Fire as recited to include a stuffer fragment would have been successful. Certainly the teachings of Ladner relating to DNA binding proteins produced in prokaryotic cells do not offer the technical basis; Fire do not suggest that their technology could include a stuffer fragment between two identical sequences, let alone any advantage in doing so; and the April 25, 2007, Office Action offers no technical basis for concluding that one of skill would expect success in including a stuffer fragment. Absent such a technical basis, an obviousness rejection cannot be proper. *KSR Int'l v. Teleflex, Inc.*, 550 U.S. ___ (2007).

Accordingly, Applicants maintain that each of claims 48, 107, 109, 110, 111 and 113 is patentable over Fire taken with Ladner, and respectfully request that the Examiner reconsider and withdraw this ground of rejection for obviousness under 35 U.S.C. § 103.

Finally, as detailed above, Applicants respectfully point out that the claimed invention was invented before the filing date of Fire, and before the filing date of the Fire Provisional. As

indicated in the Declarations, Applicants invented their invention prior to the filing of the Fire Provisional.

8. Disclosure of Patent Applications and Proceedings

Co-pending Patent Applications

Applicants note that there are seven other co-pending patent applications that claim priority to the '099 patent. Pursuant to Applicants duty of disclosure under 37 CFR § 1.56, Applicants disclosed each of the applications in Information Disclosure Statements filed for each of the other applications.

In addition, Applicants bring to the Examiners attention four other pending patent applications that are commonly owned by the owner of the subject application and have overlapping inventors, specifically:

US Application No. 09/287632, U.S. Publication No. 2004-0214330

US Application No. 11/364183, U.S. Publication No. 2006-0178335

US Application No. 11607062, U.S. Publication No. 2007-0078105

US Application No. 11/841737.

Applicants will bring to the attention of the Office any other related applications that may be filed in the future in accordance with their duty of disclosure.

Prior or Concurrent Proceedings

Applicants duly inform the Examiner of the ruling of the U.S. Court of Appeals for the Federal Circuit (CAFC) to the appeal of the U.S. District Court of Delaware's decision in *Benitec Australia, Ltd. v. Nucleonics, Ltd.*, No. 04-0174 (D. Del. September 29, 2005) (order

granting Benitec's Motion for Voluntary Dismissal Without Prejudice). The CAFC affirmed the ruling of the District Court in granting Benitec's motion to dismiss. *Benitec Australia, Ltd. v. Nucleonics, Ltd.*, No. 06-1122 (Fed. Cir. July 20, 2007). This litigation involves a claim of patent infringement of Patent No. U.S. Patent No. 6,573,099. Benitec is a co-assignee of the '099 patent with the CSIRO, the assignee of the subject application. On October 11, 2007, the CAFC denied a Petition for Rehearing and Rehearing *En Banc* filed by the defendant/appellant Nucleonics, Inc.

In addition, in an appeal hearing of the Technical Board of Appeal of the European Patent Office (EPO) on April 24, 2007, regarding a European patent application related to the '099 patent (EP1071762), the EPO rejected the patent application for formal technical reasons unrelated to substantive enablement or obviousness issues. (Appeal No. T1491/05-3308). The claims are being pursued in Europe in divisional applications.

Applicants have filed concurrently an Information Disclosure Statement that includes these decisions with copies for the Examiner's review.

9. Conclusion

In view of the above amendment, Applicants believe the pending application is in condition for allowance and requests favorable action on the merits. Should the Examiner feel that any issues remain, Applicants request that the Examiner contact the undersigned so that the issues may be expeditiously addressed and prosecution of the instant application continue.

Applicants submit concurrently a request for a three-month extension of time under 37 C.F.R. § 1.136 and the accompanying fee, and a request for continued examination under 37 C.F.R. § 1.114. Please charge our Credit Card in the amount of $1,860.00 covering the fees set

forth in 37 C.F.R. §§ 1.17(e) and 1.136(a). Credit Card Payment Form SB-2038, with a signature from an authorized cardholder, is enclosed. In the event that any additional extension of time is necessary to prevent the abandonment of this patent application, then such extension of time is petitioned. The U.S. Patent and Trademark Office is authorized to charge any additional fees that may be required in conjunction with this submission to Deposit Account Number 50-2228, referencing matter number 025122.0101N1US, from which the undersigned is authorized to draw.

Dated: October 29, 2007

Respectfully submitted,

By _____

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